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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,010	02/11/2004	Carsten-Peter Carstens	25436/1344	3414

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,010	CARSTENS, CARSTEN-PETER	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 45-61 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 45-61 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 2/04; 9/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

The amendment filed 11/2/2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NOs 14-16. There is no support for the entirety of these sequences in the specification as filed (SEQ ID NOs 14 and 15 are 10 Kb, and SEQ ID NO 16 is 1.1. Kb). If they are the GenBank Accession Nos. referenced on pages 23 and 24 of the specification, in the context of the specification the Accession Nos. are used only to indicate where within the Accession Nos the specific primers in the PCR anneal, it is not even disclosed that the Accession Nos. were the actual PCR template (e.g. page 23, lines 19-26). Hence, the only support found for any sequences from these Accession Nos. is the inherent support that the PCR primers used in the specification anneal at specific regions in the Accession Nos. This does not provide support for entire Accession Nos., which, at best, appear to be what is contained in the Sequence Listing.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50-52 and 59-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 50-52 and 59-61 recite tRNA sequences comprising sequences found between specific base pairs of Genbank Accession Nos. The specification provides no guidance on which, if any, of the SEQ ID NOs in the Sequence Listing corresponds to the Genbank Accession Nos. recited in the claims. Furthermore, because the content of Genbank entries can (and do) change over time due to corrections, it cannot be determined if the sequences represented by the SEQ ID NOs (if they are the recited Genbank Nos.) are the actual DNA sequences as they existed at the time of filing of the instant application (applicants claim priority to 1999). Therefore, it cannot be determined what the actual tRNA sequences must be in order to anticipate the claims, preventing a satisfactory search of the claims. Thus, the metes and bounds of the claimed subject matter are unclear, and a search of the prior art regarding these specific sequences cannot be performed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-52 and 59-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The recitation of tRNA sequences comprising sequences of Genbank Accession Nos. in claims 50-52 and 59-61 is an attempt to incorporate essential, claimed subject matter by reference to prior art documents (i.e. the Genbank entries). A review of the disclosure as filed does not reveal these DNA sequences, thus there is no evidence applicants had possession of these specific DNA sequences. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. See MPEP §608.01(p) (I). Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The attempt to incorporate subject matter into this application by reference to the Genbank Accession Nos. recited in claims 50-52 and 59-61 is ineffective because the Accession Nos. are non-patent prior art documents (i.e. not a U.S. Patent or published U.S. application). The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with

respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45-48, 53-56, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (cited in the IDS of 2/11/2004) in view of Nakamura et al, Zhang et al, Saier, Kawakami et al, Clouthier et al (see applicants' exhibits A-G in the response filed 9/26/2002 in parent application 09/492,590) and Sprinzl et al (Nuc. Acids Res., 1998).

Del Tito et al teach the construction and use of a plasmid, pRI952, which comprises an array of two tRNA genes (argU and IleX) encoding tRNAs specific for the rarely used codons AGG/AGA and AUA, respectively (e.g. page 7087, paragraph 2; Tables I and II). The authors teach that PRI952 was constructed by insertion of a PCR-amplified DNA comprising the gene (comprising the endogenous tRNA promoter) for ileX flanked by HindIII restriction sites into

pDC592, a pACYC184 derivative (i.e. low copy number plasmid comprising the *tet* promoter and chloramphenicol resistance gene, see description and diagram of pACYC184, GenBank accession number X06403) already possessing the argU gene (e.g. pages 7087, column 2, paragraph 2). Del Tito et al teach that coexpression of the two tRNA genes along with the gene encoding the heterologous polypeptide Mup^r IRS results in increased levels of active protein as compared to a control in which no additional tRNA genes are expressed or as compared to cells comprising a plasmid only expressing the ileX gene (e.g Table II). Del Tito et al teach that "...problems in expression can be avoided by a careful inspection of the coding sequence and inclusion of appropriate tRNA genes or necessary site-specific mutations." (page 7087, column 1, paragraph 2). The authors conclude that the co-expression of minor tRNAs such as ileX or argU can be utilized to overcome translational stresses due to the presence of rarely used codons within the coding sequence for a gene of interest (e.g. page 7091, column 1, paragraph 3). Del Tito et al teach the purification by reverse-phase HPLC of another heterologous polypeptide (i.e. the B/LeeHA antigen) produced by their system for compensating for the presence of rare codons in the coding sequence for the desired polypeptide (e.g. page 7088, column 1, paragraphs 3-4).

Del Tito et al do not explicitly teach the use of a vector comprising an array of the three tRNAs argU, ileY, and leuW.

Nakamura et al (Nucleic Acids Research, 1996, Vol. 24, pages 214-215; see the entire reference) provide codon usage data tabulated from the GenBank international DNA sequence databases for 4,805 species (e.g. prokaryotes, protozoa, fungi, animals and plants).

Zhang et al (Gene, 1991, pages 61-72, see the entire reference) detail low usage codons in species as diverse as E. coli, yeast, Drosophila and primates.

Saier, M. H. (FEBS, 1995, Vol. 362, pages 1-4; see the entire document) teaches the rare codon usage in several different species (e.g. R. capsulatus, R. speriodes, C. acetobutylicum, S. coelicular and E. coli).

Sprinzl et al (Nucleic Acids Research, 1998, Vol. 26, , pages 148-153); see the entire document) teach a compilation of 3,279 sequences of tRNA genes (including the *E. coli* argU, ileY, and leuW genes) including cellular and mitochondrial tRNAs from bacteria and phage, plants, yeasts and fungi, insects, amphibians and mammals, including rats, mice, cows and humans.

Kawakami et al (1993, Genetics, Vol. 135, pages 309-320; see the entire document) teach a rare Arg-tRNA-CCU in S. cerevisiae).

Clouthier et al (J. Bacteriology, 1998, Vol. 180, pages 840-845, see the entire document) teach a rare Arg-tRNA-AGA from S. enteritidis.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the vector construct taught by Del Tito et al for compensating for the presence of rarely used codons present in the gene encoding a protein of interest by interchanging and/or adding different tRNA genes corresponding to other rarely used codons in a given cell type, because Del Tito et al teach that it is within the skill of the art to carefully scrutinize the coding sequence of a protein, identify rarely used codons and compensate for the presence of such rarely codons by supplying in trans the tRNA corresponding to the identified rarely used codons from a vector expressing different tRNA genes, and because the rarely used codons and corresponding

genes were widely known in the art (i.e. the teachings of Nakamura et al, Zhang et al, Saier, Sprinzl et al, Kawakami et al and Clouthier et al). One would have been motivated to do so in order to meet the particular rare-codon requirements of a gene encoding a desired protein in combination with a given cell type, and thus receive the expected benefit of increasing its expression in the given cell type, as taught by Del Tito et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing any tRNA gene obtained from any cell type that was known in the art (i.e. ileY, proL, leuW, etc.) in the approach taught by Del Tito et al to increase the production of a desired protein that comprises rarely used codons.

Regarding the limitations of instant claims 46, 47, 55, and 56, these are matters of design choice in the preparation of the vector. Del Tito et al teach the insertion of the ileX gene, flanked by HindIII sites, into the pDC592 vector. Thus, the gene could have been inserted in either orientation relative to the argU gene. Such choices are dependent upon the method steps used to construct the vector, the sequence of the tRNA gene chosen, and the location of convenient restriction sites in the chosen vector. Applicants choice of an order of argU, ileY, and leuW appears arbitrary from a reading of the specification and imparts no discernable advantage to the vector. The same is true for the orientation of the ileY gene relative to the other tRNAs. Given that the basic concept that is the crucial element of the invention was already known in the art (i.e. providing tRNAs corresponding to rarely used codons from DNA constructs comprising the cognate tRNA genes), that applicants' invention differs only in the make-up of the DNA constructs that are used to express the tRNA genes, and that the means and materials for making the changes necessary to the constructs taught by Del Tito et al in order to

arrive at the claimed invention, it is the examiner's conclusion that there is no significant contribution from the instant application that was not already readily available from the prior art.

Claims 49 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al, Nakamura et al, Zhang et al, Saier, Kawakami et al, Clouthier et al, and Sprinzl et al as applied to claims 45-48, 53-56, and 58 above, and further in view of Skerra et al (U.S. 5,849,576, 1998).

The teachings of el Tito et al, Nakamura et al, Zhang et al, Saier, Kawakami et al, Clouthier et al, and Sprinzl et al are as above and applied as before, except: Del Tito et al teach that the expression of tRNA genes has been shown to be deleterious to the host cell and that for this reason the ileX promoter was used to control expression of the ileX gene from low-copy number plasmids (page 7090, column 2, ¶ 3).

None of the above references teach the use of the *tet* promoter operably linked to the tRNA genes.

Skerra et al teach the use of the *tet* promoter to control expression of toxic genes in *E. coli* (see entire document, particularly the abstract and column 2, lines 49-55).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the *tet* promoter (and the regulable tetracycline expression system) described by Skerra et al with the vectors of Del Tito because Del Tito et al teach that the expression of tRNA genes in *E. coli* can have a negative effect on the host cell. Skerra et al teach that a system for the tightly controlled expression of target, toxic genes in *E. coli* was well known and widely used within the art for the expression of toxic genes in *E. coli*. One would have been motivated to do so in order

to receive the expected benefit of avoiding any potential toxic effects associated with the expression of the tRNA genes in *E. coli* during periods when expression of said tRNA genes was not required. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing the *tet* promoter expression system for the controlled expression of tRNA genes in *E. coli* for the purpose of expression of desired polypeptides whose coding sequence comprises a number of different, rarely used codons.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 54 and 58 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The nucleic acid is not recited as purified or isolated, and thus reads on the *E. coli* genome, a product of nature. According to the specification and claims, the *E. coli* genome contains all three of the tRNA genes specified in the claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER